## REMARKS

Claims 21-26, 28-33, and 35-36 remain in the present application. Claim 37 is new. Claims 1-20, 27, and 34 have been previously canceled without prejudice. No additional claims fee is believed to be due.

Claim 21 has been amended to delete therefrom reference to specifically defined hydrophilic, water-miscible, anhydrous solvent materials.

Claim 21 has also been amended to more specifically recite that the claimed oral composition comprises from about 1% to about 10% by weight of added water. Support for this amendment is found in the specification at page 8, lines 33-34, and page 9, lines 1-2.

Claim 37 has been added to recite specifically defined hydrophilic, water-miscible, anhydrous solvent materials. Support for this amendment is found in canceled Claim 34.

### Examiner Interview

Applicants undersigned agent gratefully acknowledge the telephone interview granted by Examiner Webman on October 28, 2003. During the interview, Applicants' representative discussed the relevance of the applied 35 U.S.C. 103 rejection in the present application. The substance of such discussion is embodied in the following remarks.

### Invention Synopsis

The present invention is directed to stable liquid compositions which comprise a pharmaceutical active and a reducing agent, wherein the reducing agent provides for improved stability of these compositions especially when the compositions are formulated into various product forms such as liquid elixirs for treating symptoms associated with respiratory illnesses.

It has been found that a reducing agent can be included in liquid compositions containing a pharmaceutical active to enhance long term stability of the composition, provided that the reducing agent is solubilized in a solvent system separately from a solvent system used to solubilize the active. The solubilzation of the reducing agent in one solvent phase, and the active in another solvent phase, results in a stable, homogenous, liquid composition that is highly effective in the delivery of pharmaceutical active ingredients.

### Formal Matters

#### a) Specification

The specification has been objected to for Applicants' alleged failure to provide support for recitation of reducing agents having a Standard Electrode Potential of $E^0$ value greater than about $\pm$ 0.119V. The Examiner contends that the specification recites at page 8 reducing agents that have an $E^0$

value that is not within a range of about equal to or greater than 0.114 v. Applicants traverse this objection.

Applicants submit that at page 8, second full paragraph, it is stated that the reducing agents have an $E^0$ value greater than about -0.119V, wherein exemplary reducing agents include thiourea and sodium thiosulphate. The reference, Pharmaceutical Preformulation by Wells is cited as an incorporated reference disclosing standard electrode potential of different reducing agents, wherein this reference states the $E^0$ value of thiourea as +0.029V, and the $E^0$ value of sodium thiosulphate as +0.050V. Applicants submit that these $E^0$ values stated by the Wells reference for reducing agents such as thiourea and sodium thiosulphate falls within the range of $E^0$ value greater than about -0.119V as stated in Applicants' specification.

**b) Claim 33**

Claim 33 has been objected to for allegedly reciting reducing agents that do not fall within a claimed range of an $E^0$ value equal to or greater than about -0.119V. Applicants will address this objection as it would apply to Claim 23 which recites specifically defined reducing agents including thiourea and sodium thiosulphate which have an $E^0$ value equal to or greater than about -0.119V.

Applicants submit that as exemplified in the incorporated reference Pharmaceutical Preformulation by Wells reducing agents such as thiourea and sodium thiosulphate have $E^0$ values that are greater than about -0.119V. Specifically, the Wells reference recites thiourea as having an $E^0$ value of +0.029V and sodium thiosulphate as having an $E^0$ value of +0.050V, wherein these $E^0$ values are within the claimed range of equal to or greater than –0.119V.

**Art Rejections**

**a) 35 U.S.C. 103 rejection over Sorrentino in view of Lin et al.**

Claims 21-26, 28-32, and 35-36 have been rejected under 35 U.S.C. 103 as being unpatentably obvious over Sorrentino (U.S. Patent 5, 100,898) in view of Lin et al. (U.S. Patent 3,996,355). The Examiner contends that it would have been obvious to incorporate the tert-butyl hydroquinone (TBHQ) of Lin et al. into a liquid composition of Sorrentino, to thereby realize Applicants' invention. Applicants respectfully traverse this rejection as it would apply to the amended claims.

Sorrentino discloses liquid pharmaceutical compositions which are suitable for oral use, and which comprises an antitussive, dyclonine, and an aqueous-based orally acceptable pharmaceutical carrier containing a co-solvent such as ethyl alcohol, propylene glycol, glycerin, polyethylene glycol, and the like. Sorrentino further discloses that the liquid pharmaceutical compositions can optionally comprise antioxidants such as butylated hydroxy anisole (BHA) or butylated hydroxy toluene (BHT). Sorrentino, however, fails to disclose a reducing agent having an $E^0$ value equal to or greater than about -0.119V.

Lin et al. disclose permanent suspension pharmaceutical dosage forms which are suitable for oral administration, and which comprise a drug dispersed in an anhydrous vegetable oil vehicle containing a saccharide as the suspending agent. Lin et al. further disclose that the suspensions also contain pharmaceutically acceptable excipients such as antioxidants selected from ascorbyl palmitate, butylated hydroxytoluene, butylated hydroxyanisole, and tertiary butyl hydroxyquinone (TBHQ). Lin et al. however fails to disclose oral dosage forms that comprise a hydrophilic, water-miscible, anhydrous solvent.

Applicants submit that a combine disclosure of the Sorrentino and Lin et al. references would not obviously lead the skilled artisan to a realization of Applicants invention of Claims 21-26, 28-32, and 35-36, as amended. First, there is no motivation to combine the Sorrention and Lin et al. references. Sorrentino teaches and suggests aqueous-based liquid pharmaceutical compositions. Lin et al. teach and suggest anhydrous suspensions and comparatively exemplify the anhydrous suspensions against aqueous suspensions. Applicants submits that there is no motivation to combine a reference that teaches aqueous-based compositions with a reference that teaches anhydrous suspensions.

Moreover, the Sorrentino reference is completely silent to teaching or suggesting Applicants' reducing agent. The Examiner contends that the antioxidants disclosed by Sorrentino are equivalent to those antioxidants disclosed by Lin et al., therefore it would have been obvious to substitute the BHA of Sorrentino with the TBHQ of Lin et al., to thereby realize Applicants invention. Applicants disagree. Nowhere does Sorrentino, Lin et al., or the common knowledge of the skilled artisan assert that TBHQ is equivalent to BHA The Sorrentino and Lin et al. references teach different fields of endeavor, and the Lin et al. reference provides no motivation to substitute the commonly disclosed BHA antioxidant. Applicants submit that the skilled artisan certainly would not look to the Lin et al. reference that teaches and suggests anhydrous suspensions for substituting a component of the anhydrous suspension into an aqueous-based compositions such as the aqueous-based liquid compositions of Sorrentino for a realization of Applicants' invention.

In view of the foregoing remarks, Applicants submit that a combined disclosure of the Sorrentino and Lin et al. references would not obviously lead the skilled artisan to a realization of Applicants' invention of Claims 21-26, 28-32, and 35-36, as amended. The rejection of these claims as being unpatentably obvious over Sorrentino in view of Lin et al. is improper and, therefore, should be withdrawn.

**b) 35 U.S.C. 103 rejection over Coapman in view of Lin et al.**

Claims 21-26, 28-33, and 35-36 have been rejected under 35 U.S.C. 103 as being unpatentably obvious over Coapman (WO 93/00072) in view of Lin et al. (U.S. Patent 3,996,355). The Examiner contends that it would have been obvious to incorporate the tert-butyl hydroquinone (TBHQ) of Lin et al.

into a liquid composition of Coapman, to thereby realize Applicants' invention. Applicants respectfully traverse this rejection as it would apply to the amended claims.

Coapman discloses a process for solubilizing at least one difficult to solubilize pharmaceutical active in a mixture of polyethylene glycol and polyvinylpyrrolidone, wherein the process does not require water as a solvent except for the minor amounts of water normally present in the pharmaceutical active, polyethylene glycol, and polyvinylpyrrolidone and/or which is absorbed from the environment. Thus, Coapman discloses that his concentrated pharmaceutical compositions are substantially free of water, wherein "substantially free of water" is defined as not containing any water, except for the minor amounts of water normally present in the materials employed in the preparation of the concentrated pharmaceutical compositions and/or which is gradually absorbed from the environment or the optional gelatin shell; i.e, less than from about 0.1% to about 8% water. Coapman further discloses that the concentrated pharmaceutical compositions optionally comprise antioxidants. Coapman, however, fails to disclose a pharmaceutical composition comprising from about 1% to about 10% by weight of added water.

Lin et al. disclose permanent suspension pharmaceutical dosage forms which are suitable for oral administration, and which comprise a drug dispersed in an anhydrous vegetable oil vehicle containing a saccharide as the suspending agent. Lin et al. further disclose that the suspensions also contain pharmaceutically acceptable excipients such as antioxidants selected from ascorbyl palmitate, butylated hydroxytoluene, butylated hydroxyanisole, and tertiary butyl hydroxyquinone (TBHQ). Lin et al. however fails to disclose oral dosage forms that comprise a hydrophilic, water-miscible, anhydrous solvent.

Applicants submit that a combined disclosure of the Coapman and Lin et al. references fails to teach or suggest the oral composition of Applicants' Claims 21-26, 28-33, and 35-36, as amended. The Coapman reference teaches and suggests concentrated pharmaceutical compositions which are substantially free of water, except for bound water from the compositional ingredients, water absorbed from the environment, and/or water absorbed from the optional gelatin shell. Lin et al. teach and suggest anhydrous suspensions. By contrast, Applicants' amended Claims 21-26, 28-33, and 35-36 are now limited to oral compositions comprising from about 1% to about 10% of water that has been added to the composition.

Moreover, Applicants submit that the incorporation of the THBQ antioxidant of Lin et al. into a composition of Coapman would still be deficient in teaching or suggesting Applicants' oral composition which now comprise from about 1% to about 10% by weight of added water.

In view of the foregoing remarks, Applicants submit that the combined disclosure of the Coapman and Lin et al. references fails to teach or suggest Applicants' now claimed oral composition comprising from about 1% to about 10% by weight of added water. Accordingly, the rejection of Claims

21-26, 28-33, and 33-35, as amended, as being unpatentably obvious over Coapman in view of Lin et al. is improper and should be withdrawn.

**Conclusion**

Applicants have made an earnest effort to place the application in proper form and to distinguish the claimed invention from the applied prior art. WHEREFORE, reconsideration of this application, withdrawal of the rejections under 35 U.S.C. 103, and allowance of Claims 21-26, 28-33, and 35-37 are respectfully requested.

Respectfully submitted,

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